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THE EFFECT OF THE ADRENAL SECRETIONS ON BLOOD SUGAR METABOLISM.

Submitted by

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INTRODUCTION

Metabolism in general, as well as in many of its details, is governed by the activity of endocrine glands, or glands of internal secretion. In the human body there are approximately six of these glands which are known to secrete directly into the blood very minute amounts of active substances. These active secretions are variously called chemical messengers, hormones, or autacoids. The best known glands of internal secretion are the adrenals, thyroids, pancreas, parathyroids, pituitary, and gonads (ovaries or testes. Each of these glands secretes into the blood one or more substances which influence the activity of some organ or organs. The chemical messengers derived from the endocrine glands may bring about extraordinary shifts in the course or rate of normal metabolism.

The mechanism of the internal secretions is complex in its mode of action. It is believed that the active substances are discharged directly into the blood through the capillary blood vessels with which the glands are well supplied, and that they pass with the circulating blood to other organs and tissues, and stimulate them to activity or bring about other characteristic changes. Their activities are often synergic and in some cases there is good reason to believe that an antagonism exists between different glands. The physiology of many of these glands is more or less intimately connected with carbohydrate

metabolism. This is particularly true in the case of the pancreas and adrenals.

Various experiments show that the adrenal secretions increase the metabolic rate. Extirpation of these glands may, therefore, lead to a lowered metabolism. The most striking effects of the internal secretions in modifying metabolism are to be noted in abnormalities which develop in diseased conditions. (58)*

In the sixteenth century the adrenal glands were observed, for the first time, by Eustachius who called them glandulae renibus incumbentes. For a long time afterwards the adrenal glands were considered of slight account and were the subject merely of anatomical study and of curious speculations. Riolanus in 1628 called them glandulae suprarenales. (7)

It is interesting to note that our earliest knowledge of the internal secretions was obtained not by purely laboratory experiments but through the observation of pathological cases. In 1849, Addison (2) observed that after a certain kind of anemia, a peculiar and fatal disease often associated with bronzing of the skin, the autopsy constantly showed lesions of the adrenal capsules. This condition now known as Addison's disease, though often associated with

*(58) pp. 353-355

tuberculosis of the adrenal glands as in the cases studied by Addison, may be due tothedestruction of these glands by any process.* Addison's disease is believed to be due to hypofunction of the adrenals, and it is probable that the more severe symptoms are the result of the destruction of the adrenal cortex.

In 1856 Brown-Séquard, (12) stimulated by the work of Addison, undertook extirpation experiments to ascertain the function of the adrenals, and announced that these glands were indispensable to life, because all of his animals including rabbits and rats, died within a few days after bilateral adrenalectomy.

CONSEQUENCES OF ADRENALECTOMY

Extirpation of the adrenal glands is usually fatal; but the time element differs in various animals. If the whole glands are removed death results. Dogs and cats rarely live more than 48 hours, if both glands are extirpated in one operation; but they may live from six to ten days if the second gland is removed several weeks after the first. Elliott (23) reported that of twenty-one cats in which both glands were excised in one operation over ninety per cent died in from 18 to 48 hours. Stewart and

*The more important symptoms are pigmentation or bronzing of the skin, excessive muscular weakness leading to prostration, mental depression and other nervous symptoms, gastro-intestinal disturbance including vomiting, atrophy of the sex organs, and hypoglycemia.

Rogoff (50) removed the adrenals from 25 dogs in two operations, and found that 90 per cent died between the fourth and sixteenth days.

Gaunt (25) studied the survival of 185 bilateral adrenalectomized rats from five different colonies, and reported that the mortality among laboratory bred rats was 95 per cent within 20.5 days with an average life-span of seven days. Animals from the fifth colony (of unknown pedigree) showed a 50 per cent survival for thirty days after adrenalectomy.

In man quick death follows lesions in the glands. (40)*

Experiments show that the loss of one adrenal is not fatal. In fact, Kuriyama (35) has even observed that the remaining gland often hypertrophies, and is able to keep the animal in a normal condition.

IMPORTANCE OF THE MEDULLA

Experimental evidence indicates that the medullary tissue is not indispensable to life and health. In some animals it is very difficult to remove by operation all chromaphil tissues; but this tissue is present mostly in the medulla of the adrenal gland and the bulk of the medulla can be removed without producing death in experimental animals.

In a personal communication Dr. Wyman stated that complete removal of the medullary tissue may be tolerated

*(40) pp. 691-694

in rats by transplantation of the glands. Both adrenals are transplanted in the abdominal muscles. Autopsy of animals in which the transplants are successful shows that the cortical tissue has regenerated while the medullary tissue has disappeared. The effects equivalent to extirpation or lack of medullary tissue may thus be investigated because rats have no accessory chromaphil tissue.

ANATOMY

Like most endocrine organs, the adrenals are subject to great variation. In man, the adrenals are two small, highly vascular organs, usually situated at the upper poles of the kidneys and both weigh together about 8 or 9 grams. Of the two, the left is usually the larger.(51) Each adrenal gland is composed of an external portion or cortex, and a central portion or medulla. The boundary between the layers of the cortex and medulla is not sharply delimited.* The cortex and medulla, however, have very little in common except their anatomical position. The differences in histological structure, in embryological development, and in comparative anatomy, indicate that these two portions of the gland serve quite distinct functions in the body. (59) **

*My observations made in experiments with rats show that the differentiation between the medulla and cortex is so marked that it can be clearly seen by the naked eye.

**(59) pp. 130-132

EMBRYOLOGY

The adrenal glands are developed from two distinct sources.

Origin of the cortex.

The cortex is derived embryologically from the epithelial cells of the mesoderm lining the body cavity. The cells of the cortex are arranged in three concentric zones or layers. The comparatively large adrenals which are found in the human fetus are due in considerable measure, to the remarkable development of the fetal cortex. The fetal cortex, although it forms the bulk of the gland at birth, undergoes a process of progressive degeneration during the last ten weeks of embryonic life. In post-natal life the inner and middle layers of the cortex degenerate. The size of the adult cortex depends on the regenerative ability of the outer cells which continue to multiply throughout life. (31)

Origin of the medulla

The medulla arises from the same embryonic structures as the sympathetic nervous system. Lutz and Case (36) have found indications of the presence of adrenalin in the gland of the chick as early as the eighth day of incubation. Positive chromaffine reactions in the mouse-adrenal were obtained by Miller (41) approximately fourteen to fifteen days after fertilization.

Accessory adrenal tissues

Accessory adrenal tissue is located in various places in mammals. Common situations for accessory cortical tissue are the retroperitoneum, the surface of the liver, the kidneys, the space between the testis and epididymis in the male, and the vicinity of the broad ligament in the female. Accessory chromaphil tissue may be found in the sympathetic ganglia, in the carotid body, and in front of the abdominal aorta.(57)*

COMPARATIVE ANATOMY

The adrenals are found in all classes of vertebrates and in most of these classes chromaphil tissue is also found outside the glands. In the lower vertebrates the cortex and medulla are entirely distinct organs. This can be seen in the Elasmobranchs where the cortical organ is separate from the medullary. The cortical tissue is here found between the kidneys and termed the "interrenal body ". The chromaphil tissue is a series of paired bodies derived from the sympathetic ganglia and arranged along the sympathetic nerves. Lutz and Wyman (37) found that the interrenal bodies corresponding to the homologues of the cortical tissue of the higher vertebrates gave negative tests for adrenalin while the chromaphil bodies always gave positive tests. They concluded that the cortical tissue of the adrenal glands of higher vertebrates is not involved in the production of adrenalin. In the higher

*(57) p.146

species the cortex and medulla become closely associated. In amphibians, in which the mesonephros persists, the adrenals are sometimes represented by small masses of tissue just above the kidneys. There is a partial connection between the medullary and cortical tissues. In reptiles and birds the two tissues become concentrated and may be found in definite locations. In mammals, these glands are well developed. The chromaphil tissue penetrates into the interrenal and is enclosed by it, forming the medulla of the definite adrenal gland. But, even in mammals in addition to the adrenals small accessory masses of chromaphil and cortical tissues are found in other regions. (40)* (57)**

BLOOD SUPPLY

In humans, blood is freely and plentifully supplied to the adrenals by the suprarenal, inferior phrenic, and renal arteries. These arteries enter the capsule of the gland and there give off many branches which supply a rich network of blood spaces in the cortex. The amount of blood passing through the glands is very large compared to their size, being about 5 - 6 cc. per gram of gland per minute in dogs and cats. Neuman (43) showed that the adrenals are probably the most highly vascularized glands in the body and that the normal blood flow

*(40) p. 690
** (57) pp 139 - 153

in the cat may reach 7 cc. per gram of gland per minute. In the higher mammalian types the greater part of the blood supplied to the gland comes first, however, into intimate relation with cortical elements. Henderson (30) has called attention to a rich network of blood spaces between the columns of cells in the cortex through which blood passes inward to very large sinuses in the medulla. Small venous channels collect the blood and discharge it into the various branches of the central vein. The lumbo-adrenal vein which emerges at the hilus empties the blood either into the vein from the kidney or directly into the large abdominal vein, the inferior vena cava.

NERVE SUPPLY

The sources of the glandular nerve supply in man are not completely known, but it is well established that the chief innervation is directly from the splanchnics. The cortical tissues are sparsely supplied with nerves and may function when entirely deprived of a nervous supply.

The medullary tissues, however, are richly supplied with nerves which entirely control the function of the medulla. (31) The secretion of the medulla of the adrenal gland is believed to reinforce the activity of the sympathetic nervous system during conditions of stress. The adrenal medulla and the sympathetic nervous system are

closely related both functionally and anatomically. The connector fibers of the splanchnic nerve can be traced into the medulla to end round ganglion cells, and also round the chromaphil cells themsleves. (59)*

COLOR REACTIONS

The two tissues of the adrenal gland give different color reactions. An exposed cortical portion has a yellowish color, but the cortical cells are not stained by potassium dichromate ($K_2Cr_2O_7$). The medulla is partly stained reddish brown after treatment with potassium dichromate. This peculiar brown stain is taken by some other cells also, and tissue so stained is called chromaphil tissue. The staining power appears to be dependent upon or correlated with the presence of the active principle of the medulla, since the amount of the hormone and the depth of stain rise and fall together. The active principle obtained in extracts of adrenal glands is quantitatively proportional to the amount of chromaphil substance.

Adrenalin, the extract of the medullary tissue, in extraordinarily minute amounts usually affects the structures innervated by the sympathetic division of the autonomic nervous system precisely as if they were receiving the nervous impulses.

*(59) p.131

ADRENALIN

The medullary portion of the adrenal glands has a particular relation to the activity of the sympathetic nervous system. Oliver and Schafer (44) reported in 1895 that the outstanding results of an intravenous injection of an extract of the adrenals in cats and other mammals, were:

(1) augmentation in blood pressure

(2) stimulation of the heart

(3) vasoconstriction in the splanchnic organs

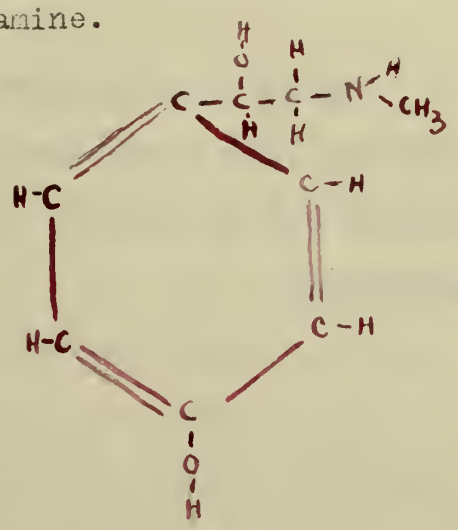
(4) the effects of the extract only lasted for a short time.

The effects produced are almost all such as are produced by stimulating the sympathetic nerves, hence the substance is said to be sympatho mimetic. Further research by different investigators showed that the substance that produced these actions was present in the medulla, and not in the cortex.

The isolation of an active principle from the adrenal medulla in an impure condition was first accomplished in this country in 1897 by Abel and Crawford (1). They obtained a monobenzoyl product and called it epinephrin. Four years later, Takamine (56) isolated the active principle from the adrenal gland in a crystalline condition. Aldrich (3) independently prepared this substance by a different method and assigned to it the empirical

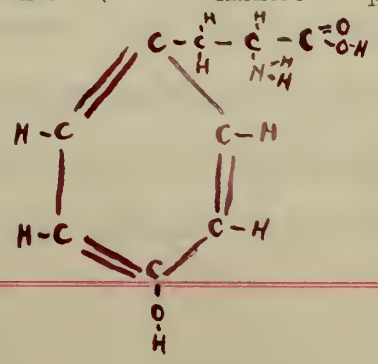
formula of $C_9H_{13}O_3N$. Jowett (32) analyzed carefully purified material and confirmed the formula proposed by Aldrich. Finally, the racemic mixture was synthesized by Stolz (52) in 1907, and later the levo-rotatory form was also synthesized.

Adrenalin has been indentified as L-3, 4-dihyroxy-phenylethanolmethylamine.



Precursor of adrenalin

While nothing is known concerning the precursor of adrenalin in the body, the fact that adrenalin is an hydroxylated aromatic derivative has favored the belief that it is synthesized by the gland, in vivo, from tyrosine. Adrenalin possesses a structure suggesting a relationship to tyrosine (α -amino - p - hydroxy phenylpropionic acid.)



Tyrosine was one of the first amino acids to be obtained from a protein. It may be prepared from casein. In fact, one investigator reported increases in the adrenalin content of the glands when they were incubated with tyrosine; but this observation could not be confirmed by others. (42)*

Adrenalin content of the glands.

Folin, Cannon, and Denis (24) determined the amount of adrenalin normally present in the adrenals of:

	Adrenalin per gm. of gld.
sheep.....	2.96 mgs
cats.....	1.36 "
cattle.....	3.96 "
rabbits.....	3.22 "
dogs and monkeys.....	2.20 "
human adults suddenly killed.....	1.00 "

Stewart (47) claimed that the amount of adrenalin in arterial blood cannot be greater than $1:3 \times 10^8$ to $1:1 \times 10^9$. The output in cats he found to be constant on an average of about 0.00025 mgs. per kgm. of body weight per minute, and the same in dogs. Cannon and his co-workers (14) who, particularly have studied adrenalin physiology estimate that much larger quantities of adrenalin are present in the adrenals, and claim that adrenalin is liberated only in

*(42) p. 413

emotional states.

ABSORPTION OF CARBOHYDRATES

The most important carbohydrate materials absorbed are the simple sugars glucose, fructose, and galactose. Polysaccharides are usually digested into simple sugars by the enzymes of the pancreas and intestine before absorption. Disaccharides may be hydrolyzed in the mucosa to glucose during their passage through the intestinal walls. The final products of carbohydrate digestion are absorbed into the blood in the form of glucose. (40)* Cori and Cori (18) reported that rats suffering from adrenal insufficiency absorb sugar slower than normal rats.

Conversion to glycogen and reversal

After glucose is absorbed, it is carried to the liver by the portal vein. If there is an immediate need for energy, the sugar passes through the liver and enters the general circulation. It diffuses from the blood into the tissues and is completely oxidized to carbon dioxide and water thus liberating a maximum of energy. If there is not an immediate need for energy, the liver cells remove the excess glucose and synthesize it into glycogen, in which form it is stored. The absorption of carbohydrates causes a rise in the blood sugar concentration, but the

*(40) p. 468

increased amount of sugar in the blood accounts for a very small fraction of that which is absorbed. The amount of glycogen in the liver increases very greatly under such conditions, and it is estimated that as much as a half-pound of glycogen can be stored in the liver of an adult. The total glycogen content of the muscles may be roughly the same as the total content of the liver.

During periods when no absorption is taking place, the tissues of the body derive energy from the glycogen which is split again into glucose and carried by the blood to the tissues. The process of formation of glycogen is called glycogenesis, and occurs most rapidly during the absorption, when the concentration of glucose in the blood is high. The reverse process called glycogenolysis takes place especially when absorption is not taking place. Evidence indicates that it is the liver glycogen (at least in the main) which undergoes hydrolysis to produce blood sugar. (58)* Presumably, both the formation and the hydrolysis of glycogen takes place under the influence of the same enzyme (glycogenase).

Normally the concentration of glucose in the blood determines to a large extent whether glycogenesis or glycogenolysis will predominate, though there are other mechanisms which control the process. (15)**

*(58) pp. 381-383

**(15) pp. 273-276

Relation of the liver to sugar metabolism.

Glycogen is normally present in the liver of well fed animals. The most important known function of the liver is to regulate the concentration of sugar in the blood. If the blood sugar becomes insufficient, liver glycogen is mobilized by impulses from the sympathetic nerves. The store of liver glycogen is utilized in the form of sugar, the fuel for the maintenance of energy processes.

Mann and Magath (38) (39) showed that in hepatectomy there is a progressive decrease of the blood sugar level. Further experiments have demonstrated that the liver must be regarded as the source of glucose in the blood, and that the muscles play little or no part in maintaining the normal level of blood sugar. Extraordinary shifts in carbohydrate balance in the organism may be brought about, however, by the secretions of the adrenals and pancreas.

Renal threshold for sugar.

In normal human subjects the glucose content of blood is about 100 mgs. in 100 cc. of blood, or 100 mgs. per cent. The variation of sugar in the blood may be from 80 mgs. to 160 mgs. per cent. The former represents the level attained on fasting for twenty-four hours, while the latter concentration may be reached after partaking of a meal rich in carbohydrates or sugar.

A rise in blood sugar above 160 mgs. per cent, causes

marked excretion through the urine. The kidneys ordinarily hold back the glucose until there is about 160 mgs. per cent of sugar, but when the sugar concentration has reached this value, it is said to have reached the renal threshold. The renal threshold varies slightly in different healthy individuals, * but in the light of many investigations the accepted figure is from 160 to 180 mgs. per cent.

If the concentration of sugar in the blood falls to 70 mgs. per cent or lower, weakness, fatigue, and hunger are manifested. Symptoms of incoordination, profuse sweating, pallor, and delirium are exhibited if the blood sugar concentration is further reduced. (15)**

ROLE OF THE PANCREAS.

The internal secretion of the pancreas (insulin) is important and indispensable to make the blood sugar available for utilization. Lesions in the pancreas are observed in cases of diabetes, and animal experiments show that removal of the pancreas brings on diabetes. A condition in which glucose is excreted rather than utilized is found in such cases. In the absence of insulin, the glucose concentration of the blood is maintained above the

* The chief value in determining the renal threshold for sugar is in connection with the diagnosis of renal glycosuria as contrasted with true diabetes.

**(15) pp. 98 - 103

kidney threshold and there is continuous glucose excretion or glycosuria.

When insulin is injected subcutaneously it produces definitely demonstrable chemical effects. The blood sugar concentration falls, depending on the dosage, to levels below normal. Some of the glycogen may disappear from the liver. If an overdose is taken, unconsciousness, convulsions, and even death may result. The effects of an overdose of insulin or hypoglycemia may be ameliorated by simultaneously eating or injecting glucose. (57)* In an excellent review, Cori (17) has emphasized that insulin and adrenalin may be factors of equal importance in regulating carbohydrate metabolism.

INFLUENCE OF ADRENALIN ON SUGAR METABOLISM.

A very important discovery made by Blum (5) was that the subcutaneous or intravenous injection of adrenalin greatly increased the blood sugar provided the liver contained glycogen. and therefore, produced hyperglycemia and glycosuria.

The adrenal glands were thus brought into relationship with glycogen conversion. Since that time much experimental work has been done in an attempt to determine the relative importance of adrenalin and the nervous system in regulating the level of blood sugar.

* (57) pp.66-69

The question that arises is whether the conversion of glycogen to glucose upon stimulating the splanchnics is due to the direct effect of the stimulus on the cells of the liver, or whether it is the indirect effect of stimulation of the adrenals, since these splanchnic nerves supply both organs. (40)*

To explain the significance of adrenalin Cannon (14) (15) has postulated the theory that this substance is secreted only during emotional stress of pain, hunger, fear, and rage, and enables the organism to cope with emergencies.

The increase of adrenalin and the increase of sugar in the blood are concomitantly reflex in character and because reflexes are generally useful responses, the secretion of adrenalin is beneficial. During emotional stress there is a mass shifting of the blood from the skin and viscera to the organs involved in neuromuscular exertion. The blood pressure is raised, the heart is steadied in rate, and made to beat more powerfully. The entire animal organism is toned up to maximum working capacity in the face of danger. As a result of these conditions, the body has to be maintained at a maximum energy level. Fear and rage, which accompany life and death struggles and flight, excite the secretion of adrenalin into the circulating blood

*(40) pp. 820-824

and reinforce the activity of the sympathetic. There is consequently a mobilization of an increased supply of ready fuel in the form of blood sugar. Emotions, therefore, stimulate the adrenals to liberate adrenalin and the prompt mobilization of sugar. It may be concluded that the adrenal glands are essential factors in emotional glycosuria.

The Harvard School of workers led by Cannon have accumulated much evidence in the last decade in support of the classical view of the effects of adrenalin in emergencies. The increased concentration of blood sugar has been attributed to the increase in the liberation of adrenalin into the blood stream which acts on the liver causing a breakdown of glycogen. Glycogen is called upon in times of need, changed and set free into the blood as sugar. In the absence of glycogen, adrenalin may even convert fats and proteins into glucose. It is believed, therefore, that the normal function of the adrenal medulla results in stimulating glycogenolysis.

In opposition to Cannon's emergency theory of adrenalin function Stewart and Rogoff (48) reported that the formation and storage of glycogen in the liver is not affected by the removal of both adrenals from rabbits. These authors also observed that extirpation of the adrenals in rats produced no essential changes in the capacity of the liver

to form and store glycogen.

Kuriyama (33) observed that the injection of adrenalin in fasting rabbits can cause an increase of the glycogen content of the liver. He also (34) made a number of determinations on rats, and found that adrenalectomized animals showed a significant disability to store glycogen when compared with normal animals.

Cori and Cori (19) reported that adrenalectomized rats and mice showed an almost complete disappearance of liver glycogen when fasted for twenty-four hours, although the muscle glycogen is scarcely affected beyond that of similarly starved normal animals. After the injection of adrenalin in rats the glycogen diminished in the body and increased in the liver. They believe that the decrease of muscle glycogen is due to its conversion into blood sugar, the excess of which is changed into liver glycogen. Hence, it is the muscle glycogen that, under the effect of adrenalin, produces the increased amount of blood sugar. They concluded, therefore, that the effect of adrenalin is more potent on the glycogen of the muscle than on the liver. Moreover Cori (17) has called attention to the fact that the injection of adrenalin does not inhibit the synthetic process of glycogenesis in the liver. He has found that liver glycogen does not entirely disappear even during prolonged starvation, but that the liver glycogen utilized is due to

the breakdown of protein, fat, and other substances into glucose. He states that until recently it was taught that adrenalin causes hyperglycemia because such an excess of sugar is formed in the liver that the capacity for sugar utilization in the tissues is exceeded.

BLOOD SUGAR LEVEL.

Cori (17) has pungently summarized the now generally accepted view that a rise in blood sugar elicits a secretion of insulin and that a fall in blood sugar below a certain level is followed by an automatic discharge of adrenalin. The mechanism of blood sugar regulation (production and utilization) is believed to be connected with the action of these two hormones.

According to Cannon (14) the body is able to control the blood sugar under abnormal conditions by bringing into action the combined efforts of the sympathetic and adrenal mechanisms. During the emotional conditions of pain, hunger, fear and rage the mobilization of sufficient blood sugar is due partly to impulses along the sympathetic nerves and partly to the additional effect of the secretion of adrenalin. It has been shown that the increased adrenal secretion is a more important factor in liberating sugar from the hepatic stores than the direct action of nerve impulses.

Cannon and de la Paz (16) were the first to show that secretion of adrenalin is stimulated during emotion. This was done by comparing the concentration of adrenalin in the blood of normal cats with the concentration observed when the cats were frightened by the barking of a dog. Cannon and his co-workers (14)* have particularly developed this phase of adrenalin effects. They have shown that nervous excitation of adrenalin secretion produces an unfailing hyperglycemia resulting in glycosuria. They have also observed a transient glycosuria in groups of students after severe examinations and at the close of important athletic contests.

The emergency theory of Dr. Cannon has been amply substantiated by the researches of many physiologists.

Elliott (22) showed that the secretion of adrenalin is controlled by the splanchnic nerves. During severe hypoglycemia there is a reflex discharge of adrenalin from the medulla; but when the adrenals are inactivated the effects are absent in spite of severe hypoglycemia.

Griffith (26) has demonstrated that strong stimulation of an afferent nerve raises the blood sugar, chiefly by activating the adrenal glands. Any center, therefore, that controls the amount of adrenalin discharged into the blood might be regarded as a center that influences carbohydrate mobilization.

* (14) pp. 49-79

Brooks (11) believes that the fact that reflex rises in blood sugar equal to those produced in animals with intact central nervous systems are obtained after extirpation of the fore-brain, mid-brain, and the anterior portion of the medulla oblongata does not indicate that the higher centers have no ability to control carbohydrate mobilization.

Edwards, Richards, and Dill (21) have observed that exercise with little or no emotional stress in normal men does not produce hyperglycemia; but when emotional factors are involved the blood sugar is increased, and glycosuria is evident.

Certain investigators failed to confirm the experimental evidence in favor of the emergency theory of adrenalin function.

Stewart and Rogoff (50) contended that there is no evidence that the rate at which glycogen is changed into blood sugar is influenced by the adrenalin output from the adrenals.

Stewart (47) stated that the best evidence for the view that the adrenalin output during emotion exerts no important function in glycogenolysis is that, after its suppression, the animals do not differ notably from normal animals in the blood sugar content or in a variety of other ways in which Cannon observed significant differences.

Experiments by Cori and Cori, (20) on the influence of adrenalin on blood sugar utilization, indicated that animals injected with adrenalin are unable to utilize glucose at the same rate as the normal uninjected animals. These experiments showed that animals supplied with adrenalin have a diminished necessity for blood sugar in the tissues.

Cori (17) has further stated that the injection of adrenalin in rats causes an accelerated disappearance of muscle glycogen and at the same time liver glycogen in the rat and rabbit is formed in excess over that mobilized, so that there is a rise in hepatic glycogen (instead of a glycogenolysis). He has found that the increase in liver glycogen, and in blood and tissue sugar may be accounted for by the disappearance of muscle glycogen under the influence of injected adrenalin.

Cannon (13) objected to experiments that tend to show continuous secretion of adrenalin because experimental evidence was obtained during disturbing conditions. He concludes that adrenalin is not secreted continuously, but only in emergencies.

It is evident from the above discussion of the medullary function that the emergency theory of adrenalin function is the accepted explanation for normal adrenalin activity in the organism. The emergency theory has now become a physiological fact.

RELATIVE IMPORTANCE OF THE CORTEX TO LIFE.

The cortex, in contrast to the medulla, is the indispensable portion of the adrenal. Death in adrenalectomized animals is due primarily to the absence of the cortical tissue. Knowledge of the functions of the adrenal cortex has been developing in recent years. Considerable evidence is available tending to show some relationship between the cortex and normal carbohydrate metabolism. Recently a hormone has been extracted from the cortex in a highly concentrated form. Animals from which all the adrenal tissue has been removed may be kept alive with these extracts.

INTOXICATION THEORY.

The terminal picture after adrenalectomy has all the symptoms of an intoxication or the final exhaustion of a reserve. The cause of the sudden death is not clearly understood. One of the explanations is that toxic protein degradation products accumulate in the blood because the normal channels of destruction and elimination are not available. It is generally found that carnivorous animals die most rapidly after adrenalectomy.

CORTEX AND BLOOD SUGAR.

In experiments with adrenalectomized rats, Kuriyama (34), Cori and Cori (18), and Artundo (4) noticed a fall in blood sugar. Artundo also found a fall in hepatic and

muscle glycogen.

Wyman and Walker (61) determined the blood sugar of a large number of normal and adrenalectomized rats. Following extirpation of the glands and coincident with the appearance of symptoms of adrenal insufficiency the blood sugar values fell from the normal average of 82 mgs. per cent to about 55 mgs. per cent while in the terminal convulsive stages levels as low as 30 mgs. per cent were reached. They reported that rats which possessed gross accessory cortical tissue, or in which successful cortical transplants had been made, the blood sugar remained within normal limits. From these results they suggested that the cortex is concerned in the steady maintenance of the blood sugar level.

According to one of the prevalent theories the cortex is the primary factor in the maintenance of a normal blood sugar level. Death after adrenalectomy has been attributed by Britton (6) to an abnormal decrease of the blood sugar. He has reported that for some days after operation the blood sugar in cats fluctuated between 70 and 90 mgs. per cent. In cats which showed slight weakness the blood sugar was found to be below the normal range, and in nearly half the cases was below 50 mgs. per cent. Observations on adrenalectomized rats, opossums, squirrels, and ground hogs showed that the blood sugar

TABLE 1*

Blood sugar level in animals (cats) showing symptoms of adrenal insufficiency.

CAT NUMBER	BLOOD SUGAR	CONDITION	CAT NUMBER	BLOOD SUGAR	CONDITION
	mgm. per cent			mgm. per cent	
252	61	Weak	350	49	Weak
255	67	Weak	357	50	Prostrated
258	43	In Convulsions	359	54	Weak
259	65	In convulsions	360	42	Weak
261	39	In convulsions	363	52	Prostrated
285	39	Weak	365	32	In convulsions
316	57	Very weak	366	41	Weak
316	47	In convulsions	375	25	In convulsions
320		Prostrated	380	52	Weak
323	56	Prostrated	381	59	Weak
338	54	Very weak	383	63	Weak
339	50	Prostrated	386	51	Weak
342	54	Very weak	388	52	Weak
344	51	Prostrated	391	33	In convulsions
346	43	In convulsions	395	32	Very weak

*Britton, S. W. Amer. Jour. Physiol. 1931 99 12

values were significantly reduced. He also noticed that corresponding to the decrease of blood sugar there was an increase of blood lactates. The fluctuation of the blood sugar concentration corresponded directly to the degree of adrenal insufficiency. (See Table 1.) Britton, therefore, claims that the cortex of the adrenal glands may be specifically concerned with the storage and utilization of carbohydrates in the body.

CORTICAL EXTRACTS.

The active principle of the adrenal cortex has been obtained with varying success. Stewart and Rogoff (51) claimed to have prepared active extracts of the cortex with lipoid solvents. They observed that their extract was not free of adrenalin, but concluded that the results obtained were not due to the presence of adrenalin. They named their cortical extract interrenalin. In adrenalectomized dogs, intravenously injected with interrenalin, the life span was prolonged five or six days over that of control animals. (46)

Hartman and his associates (28) made salt extracts of the adrenal cortex which prolonged the life of cats for twenty-two days or five times the length of an untreated animal. They proposed the name cortin. Hartman used fresh beef adrenals which had been chilled soon after removal from the animal. The extract was not very potent; but it

contained the active principle of the cortex. Cortin when injected into adrenalectomized rats increases metabolism.

Hartman, Brownell, and Crosby (27) by the use of cortin, have verified the evidence of Wyman and tum Suden (60) that the loss of the adrenal cortex rather than of the medulla is responsible for the lower resistance to cold after adrenal extirpation, and that adrenalectomized rats could be protected against short exposure to cold by autoplastic cortical transplants. They determined the blood sugar in rats after cooling and found that low temperature and low blood sugar have no definite relation.

Hartman, Brownell, and Lockwood (29) have reported that the administration of cortin diminishes mental fatigue, improves sleep, increases resistance to toxins, increases heat production, brings back normal metabolism, and raises the low blood sugar frequently encountered in the late stage of adrenal insufficiency. They suggest that cortin is a general tissue hormone. If cortin is discontinued in animals with complete adrenal insufficiency or in man with marked insufficiency, it is usually two or three days, sometimes longer, before the symptoms begin to reappear.

Swingle and Pfiffner (53) prepared a cortical extract from beef by the use of alcoholic benzene. The extract is very low in adrenalin content and very effective in combatting adrenal insufficiency. This extract may be injected subcutaneously. It is practically free of adrenalin.

The preparation of the Pfiiffner and Swingle (45) potent extract of beef adrenals may be injected subcutaneously, intraperitoneally, and intravenously. They reported that it can replace complete adrenal cortex insufficiency of animals. Swingle and Pfiiffner (55) extracts preserved with 0.1 per cent benzoic acid retain their potency for long periods at room temperature; but are thermolabile by boiling for two minutes.

As stated above Britton and Silvette (10) have recently reported that the prepotent function of the adrenal cortex is to regulate the carbohydrate metabolism. They (9) used a modified Swingle and Pfiiffner (53) extract and further reduced the amount of adrenalin present. Their extract increased the blood sugar when administered intraperitoneally and produced similar changes when from three to five times as much was given orally (8). Reports by these authors indicate that adrenalectomized animals, showing symptoms of the severest insufficiencies, may be brought to normal when cortico-adrenal extracts are injected. After injection, the blood sugar rises gradually and reaches a maximum at the end of the fourth hour. In some cases the rise is to a normal level and in others to 100 mgs. per cent or higher. A gradual decline may be observed at the end of 24 to 48 hours after injection.

They noted that the blood lactates are much increased in the cases of adrenal insufficiency, and that the decrease

of lactates is brought about, along with the increase in blood sugar, by injections of cortico-adrenal extract.

Intraperitoneal injections of the extract into normal cats, rabbits, and rats increased the blood sugar according to Britton and Silvette (9). They observed that the larger the amount of extract injected into operated cats, the greater is the increase in the blood sugar. In general the blood sugar raising power of the extract is a direct function of the amount injected and of the elapsed time after adrenalectomy. (See Table 2.) They found that injections of adrenalin corresponding to the amount present in the extract produced only small increases in blood sugar and that the changes were transitory. The action of glucose solution was only slightly palliative. An intraperitoneal dose of extract represented in cortical tissue from two to three thousand times the amount present in a normal cat. Such a dose lasted from 24 to 48 hours and the hypoglycemic conditions again set in unless re-injections were given. Nocuous effects were not observed when such relatively huge amounts of the extract were given intraperitoneally, subcutaneously, intravenously, or intracardially in one or more doses in the course of about twelve hours.

TABLE 2**

Blood sugar changes in adrenalectomized cats following injection of cortico-adrenal extract.

In all cases the animals showed symptoms of insufficiency.

CAT NUMBER	DATE	AMOUNT EXTRACT GIVEN	BLOOD SUGAR Before Injection	BLOOD SUGAR After Injection	Increase in blood sugar	TIME BETWEEN INITIAL And FINAL BLOOD SAMPLES
		cc. per kgm.	mgm. %	mgm. %	%	hours
255	10/28/30	4	67	94	40	3.0
285	3/3/31	9	39	100	156	18.5
321	2/4/31	8	69	80	16	3.5
323	2/5/31	6	56	68	21	8.0
339	2/16/31	10	50	61	22	4.5
346	2/18/31	10	43	80	86	4.0
350	3/3/31	19	49	135	176	12.0
363	3/2/31	17	41	52	21	12.0
365	3/2/31	8	32	79	147	13.5
366	3/3/31	11	41	147	258	11.0
374	3/9/31	5	34	44	30	1.5
375	3/9/31	5	34	44	30	1.0
375	3/10/31	10	40	100	150	13.0
375	3/12/31	10	27	37	37	5.0
386	3/19/31	30*	65	87	34	24.0
388	3/29/31	10*	52	66	37	18.0
388	4/2/31	20*	57	92	61	2.5
389	4/10/31	20	54	98	66	25.0

TABLE 2**

Blood sugar changes in adrenalectomized cats following injection of cortico-adrenal extract.

In all cases the animals showed symptoms of insufficiency.

CAT NUMBER	DATE	AMOUNT EXTRACT GIVEN	BLOOD SUGAR Before injection	BLOOD SUGAR After injection	BLOOD SUGAR Increase in blood sugar	TIME BETWEEN INITIAL And FINAL BLOOD SAMPLES
		cc. per kgm.	mgm. %	mgm. %	%	hours
398	4/10/31	20	60	84	40	8.5
444	5/18/31	20*	47	159	217	7.0
444	5/25/31	20*	43	147	241	7.5

*Extract given by mouth; all other injections given intraperitoneally.

** Britton, S. W. & H. Silvette Amer. Jour. Physiol. 1931 99 21

That these cortical preparations have a practical value is established by the facts that they are able not only to prolong indefinitely the life of an adrenalectomized animal, but also to restore it to normal even from the severest symptoms of adrenal insufficiency. Cortin has already proved its value as the specific treatment for the hitherto fatal Addison's disease. The prohibitive cost of cortical extracts and the potential lack of adrenals leaves to the chemists the discovery of the formula of the hormone so that a synthetic product, less expensive and thus more available for the relief of human suffering, may be made.

SUMMARY

1. The anatomy and embryology of the adrenal glands are described.

2. The medulla and cortex though anatomically related are functionally distinct.

3. The active principle of the medulla has to do with rapid adjustments and changes.

4. Adrenalin accelerates the mobilization of blood sugar, the energy fuel par excellence.

5. While adrenalin is not indispensable to life and health, the organism which can muster its energies is most likely to survive. At times of great emergency adrenalin serves normally to integrate the body for strenuous muscular activity.

6. Cannon believes that adrenalin acts primarily on the liver glycogen; but Cori and Cori conclude that the basic action of adrenalin is to accelerate muscle glycogenolysis.

7. About all that is known concerning the function of the adrenal cortex is that it is essential for life.

8. The cortex is concerned with the steady maintenance of certain body conditions either by its ability to control the production or elimination of poisonous waste products or by the maintenance of a normal blood sugar level.

9. Active extracts of the adrenal cortex have been prepared which restore to health totally adrenalectomized animals suffering from severe adrenal insufficiency, and maintain them indefinitely in good condition.

10. These extracts restore and maintain animals at a normal blood sugar level.

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